

Cardiovascular Actions of Palladium Compounds in the Unanesthetized Rat

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The natural occurrence of palladium (Pd) is rare. It is obtained as a by-product during the extraction of platinum and, until the present time, its uses were small in number—principally in the manufacture of jewelry, dental alloys, chemical catalysts, and electrical contacts. Interest in Pd toxicology has been limited to occupational exposures and even that has been sparse. Recently Pd has been chosen as one of the metals to be incorporated into the automotive catalytic converter material.

Palladium chloride has been shown to be extremely toxic when given to rabbits intravenously. Animals rapidly injected quickly died with damage chiefly to the heart. This heart damage was not explained or further defined, and other references addressing this subject have not been found. The objective of our study was to investigate and attempt to characterize toxic actions of soluble Pd compounds on the cardiovascular system of the unanesthetized rat. Surgically prepared rats were monitored for ECG, aortic blood pressure, cardiac contractility (dp/dt), and respiration before, during, and 1 hr following intravenous injections of Pd^{2+} salt solutions.

Our findings indicate that injected Pd^{2+} profoundly disturbs the electrical integrity of ventricular myocardium. Effective doses induce cardiac arrhythmias with the consequential fall in blood pressure; the extent of the response is dose related.

An immediate cardiovascular effect is seen when doses of 0.4 mg/kg or more of Pd ion as $PdSO_4$ is administered over a 40-sec period of time via the femoral vein. $Pd(NO_3)_2$ and $PdCl_2$ appear to have similar activity. To achieve an equal response three times as much Pd is necessary as $(NH_4)_2PdCl_6$ or K_2PdCl_6 .

Introduction

Palladium (Pd), discovered by Wollaston in 1803, entered industry as a useful metal in 1919 (1). It occurs in association with platinum and is recovered as a by-product in the extraction of platinum from the residues of copper and nickel refineries. Previously Pd was used in limited quantities, principally for the manufacture of electrical contacts, dental alloys, chemical catalysts, and jewelry (2). Toxicological information concerning the metal is meager and there is no known report on human toxicity from industrial exposure. Currently there has been interest generated in health

effects of Pd because of its use in the automotive catalytic converter.

It has been used for humans therapeutically, but ineffectively, for tuberculosis, gout, obesity, and as a skin germicide. $Pd(OH)_2$ injected subcutaneously, 5–7 mg/day for 3 months, as a remedy for obesity, resulted in weight loss and fever (2). A buffered $PdCl_2$ solution of 1 mg/ml, when applied as a patch test, did not cause skin irritation after 24 hr (1). The few studies carried out on animals have shown that subcutaneous injections into rabbits (3) and rats (4–24 mg/kg body weight) (1) caused no ill effects. Schroeder and Mitchener (4) fed mice $PdCl_2$ in their drinking water (5 ppm) from birth to death. This compound appeared to enhance the incidence of tumors but showed little cellular toxicity in terms of weight gain. Orestano (3) found that 18.6 mg/kg of $PdCl_2$, when given intravenously in

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small doses to rabbits, would prove fatal after 12 days with damage to kidney, bone marrow, and liver, but if given rapidly, 0.6 mg/kg caused death with damage chiefly to the heart. Meek (1) found that 0.5–1.7 mg/kg given intravenously to rabbits resulted in loss of appetite with reduced urine and feces output. The animal which received 1.7 mg/kg died after 17 days.

The objective of the present study was to investigate and attempt to characterize toxic actions of palladium compounds on the cardiovascular system of the unanesthetized rat. Intravenous injections of PdSO_4 , PdCl_2 , $\text{Pd}(\text{NO}_3)_2$, $(\text{NH}_4)_2\text{PdCl}_4$, and K_2PdCl_4 were studied.

Methods

Male Sprague-Dawley rats (300 ± 50 g) were surgically prepared 1 day prior to use. Surgery consisted of inserting polyethylene tubing (PE 50) into the abdominal aorta and (PE 10) into the femoral vein. Both catheters were guided through subcutaneous tissue and exteriorized at the back of the neck via a puncture wound through the skin. The aortic catheter was used for measurement of blood pressure and the venous catheter for injection of test solution. Six small silver electrodes, fitted with micro-strip connector pins, were inserted under the skin and sutured. These electrodes were arranged laterally so that four were near the limbs to record the ECG (lead I) and two were arranged on the lateral surface of the rib cage for respiratory

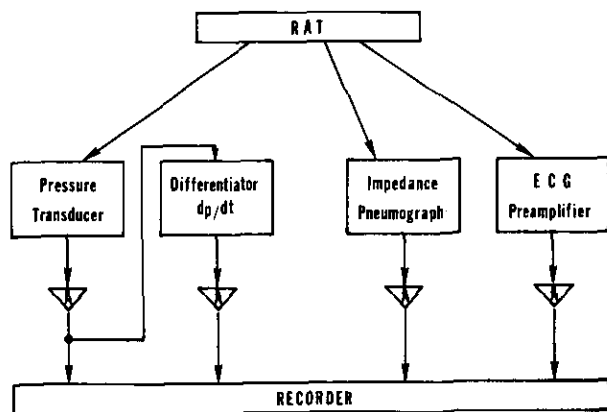


FIGURE 1. Block diagram of recording system. Pressure transducer for measurement of arterial blood pressure, calibrated with a Hg manometer (Miller Instruments); differentiator for a record of maximum rate of change of aortic pressure, time constant of 1 msec, calibrated with an oscilloscope; impedance pneumograph for record of rate and relative depth of respiration (Narco Bio-Systems); ECG preamplifier (Grass); polygraph: (Grass 7C).

measurements. Following surgery, animals were returned to their cages and given food and water *ad libitum* (Purina Lab Chow and tap water). For testing, the animals were placed in a tubular plastic holder and sensor leads were connected to the recorder. Details of the measurement system are seen in Figure 1. Rats were monitored for a 30-min control period, injected, and then monitored for the next 60 min.

Palladium compounds were dissolved in water and diluted in saline just before the injection. The Pd concentration of solutions were determined by atomic absorption with the use of a heated graphite atomizer. Analysis were repeated a number of times on each solution throughout its period of use. The total injection volume was 0.5 ml, and it was infused over a 40-sec period of time. The fitness of venous catheter was verified at the end of each experiment by introducing a lethal dose of sodium pentobarbital through it and monitoring the response.

Twelve control animals were injected with saline. PdSO_4 was the major compound studied; 41 rats were administered doses ranging from 0.25–2 mg/kg of the palladium ion. Once the toxicity pattern for this salt was established, dose levels for the remaining compounds were efficiently selected. Nine rats were dosed with $\text{Pd}(\text{NO}_3)_2$, six with PdCl_2 , 21 with $(\text{NH}_4)_2\text{PdCl}_4$, and eight with K_2PdCl_4 .

Figure 2 shows a typical polygraph recording from a control period. This type of regularity, i.e.,

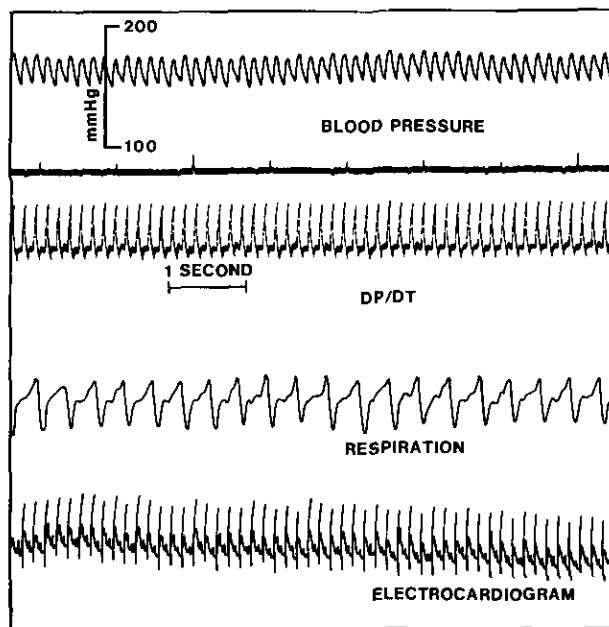


FIGURE 2. Typical control-period polygraph recording from the unanesthetized rat.

stable blood pressure, dp/dt , respiration was required for the animal to be used as a test subject. Control period values for all animals used in the study were: systolic blood pressure, 145 ± 17 ; diastolic blood pressure, 104 ± 16 ; breathing rate, 127 ± 27 ; and heart rate, 443 ± 39 . The ECG pattern, breathing amplitude, and dp/dt were measured for relative changes before and after the injection. No changes were noted in saline-injected animals.

Results and Comments

Intravenously injected PdSO_4 , $\text{Pd}(\text{NO}_3)_2$, PdCl_2 , $(\text{NH}_4)_2\text{PdCl}_4$, and K_2PdCl_4 solutions exerted immediate cardiovascular actions in the unanesthetized rat. The most constant pharmacological effect seen was the rapid induction of ventricular arrhythmias. Other alterations appeared to be dependent upon the severity of this event. In toxic doses, a premature ventricular contraction, followed by a compensatory pause, did not usually influence the blood pressure significantly; however, ventricular tachycardia or ventricular contractions originating from multiple foci often progressed into ventricular fibrillation terminating in death of the animal. Ventricular arrhythmias were not preceded by any obvious change in blood pressure. ECG pattern, or

breathing. Records following mild toxic doses were found to be in normal limits with the exception of an occasional premature ventricular contraction. Figure 3 shows a tracing of the occurrence of arrhythmias following an injection of PdSO_4 ; Figure 4 is a record of events subsequent to a lethal dose of PdCl_2 . Effects from injected palladium compounds were rated (Table 1) as to their capability for producing changes in the ECG and or hemodynamics of the unanesthetized rat. Effects were plotted against the total dose of palladium ion for each compound (Fig. 5).

When the assigned effects values were plotted against dose, the distribution of these points could be fitted to a series of S-shaped curves (Fig. 5). PdSO_4 , $\text{Pd}(\text{NO}_3)_2$, and PdCl_2 appeared to have similar pharmacological activity, where as the complex divalent compounds $(\text{NH}_4)_2\text{PdCl}_4$ and K_2PdCl_4 were comparable to each other but less potent than the simple palladium salts. A mean dose of palladium, causing mild effects was 0.4 ± 0.2 mg/kg, when administered as PdSO_4 , and 1.2 ± 0.3 mg/kg as $(\text{NH}_4)_2\text{PdCl}_4$; severe effects were seen at

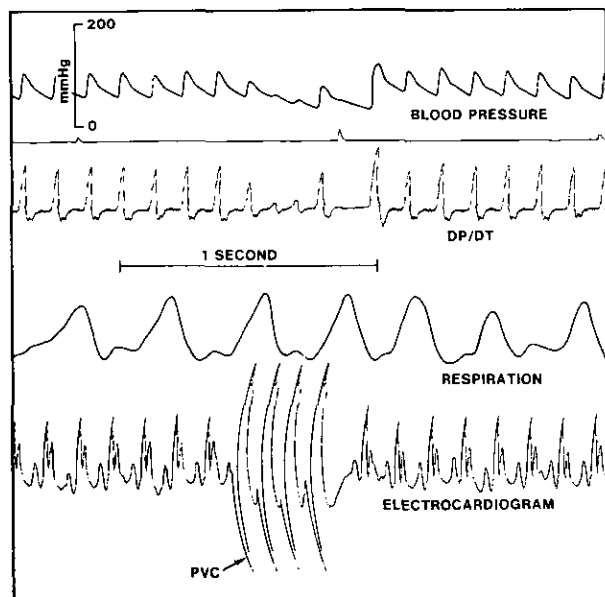


FIGURE 3. Recording of a mild toxic event following an intravenous injection of 0.5 mg/kg of Pd in as PdSO_4 . Blood pressure values dropped during the ECG irregularities but recovered once a normal depolarization pattern resumed. Breathing was not affected.

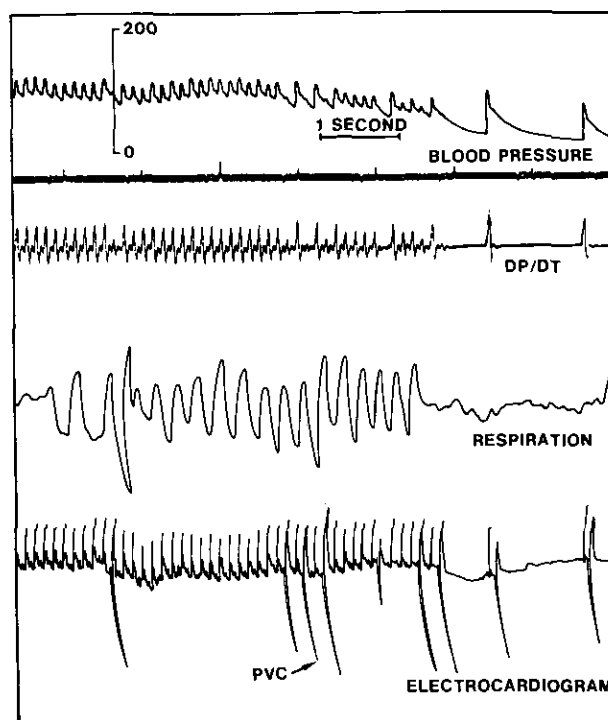


FIGURE 4. Lethal effects of an intravenous injection of 1.0 mg/kg of Pd ion as PdCl_2 . Numerous preventricular contractions followed the injection, resulting in a precipitous fall in blood pressure.

Table 1. Rating system used for palladium compounds.

Number Assigned	Effect
0	No changes from control values in the ECG, blood pressure, dp/dt or breathing for 60 min following the injection
1	Cardiac arrhythmias without a consequential fall in blood pressure or a measurable change in the ECG (most often seen as occasional ventricular premature contractions); blood pressure, dp/dt , and breathing maintained at control values for 60 min following the injection
2	Occurrence of multiple forms of arrhythmias with concomitant decreases in blood pressure; life-threatening situation for a period of time; however, the animals survived for 60 min following the injection
	Abnormal ECG patterns and blood pressure readings greater than control values were frequent residual consequences
3	Death of the animal
	Usually ECG evidence of ventricular tachycardia, with impulses often originating from more than one focus and terminating in ventricular fibrillation until hypoxia developed

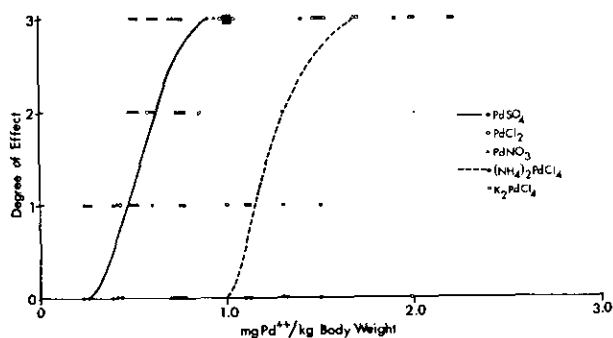


FIGURE 5. Effects of intravenously injected palladium on the unanesthetized rat (none, mild, severe, death effects; described in the text). Comparison of five different water soluble compounds. $PdSO_4$ and $(NH_4)_2PdCl_4$ are significantly different; $p < 0.005$.

levels of 0.06 ± 0.1 and 1.7 (one animal) mg/kg , respectively. Responses to the two compounds were significantly different ($p < 0.005$).

To summarize, the commercial use of palladium is expanding rapidly, possible due to the innovation

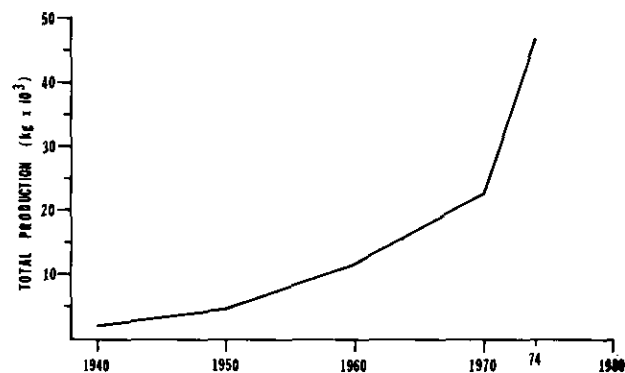


FIGURE 6. Palladium used in the United States from both domestic and foreign mine sources. The 1940 point was taken from Meek (1), whereas the remainder of the information was supplied by the U.S. Bureau of Mines, Division of Non-Ferrous Metals.

of the automotive catalytic converter (Fig. 6). Thus, it has become important to clarify its pharmacologic actions and or toxic properties. In the past little effort has been spent on the toxicology of palladium compounds. Two separate studies have shown rapid death following intravenous injections of $PdCl_2$ (1, 3). Although damage to the heart was indicated (3), the mechanisms underlying the effects were poorly understood and no general assumptions were made by the investigator. The present study has indicated that number of water-soluble palladium salts will quickly disrupt the electrical integrity of the ventricular myocardium of the unanesthetized rat. The palladium divalent ion when tested as a simple salt [$PdSO_4$, $Pd(NO_3)_2$, or $PdCl_2$] appeared to have three times the potency than when tested as a more complex compound $(NH_4)_2PdCl_4$ or K_2PdCl_4 .

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